REMARKS

This paper responds to the Office Action dated August 29, 2008.

I. The disclosure was objected to as missing a section entitled "Brief Description of Drawings."

II. Claims 1-4 were objected to containing non-elected subject matter.

III. Claims 1 and 4 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

IV. Claims 1-4 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

V. Claims 1, 3 and 4 were rejected under 35 U.S.C. § 102(b) for anticipation by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Ahrndt et al. (U.S. Patent No. 5,958,951).

VI. Claims 1-4 were rejected under 35 U.S.C. § 102(b) for anticipation by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Andersen et al. (J. Med. Chem., pg. 1717 and 1722, 2nd column).

VII. Claims 1-4 were rejected under 35 U.S.C. § 102(b) for anticipation by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Gronvald et al. (U.S. Patent No. 5,010,090).

Claim 1 has been amended to recite that the tiagabine hydrochloride is Polymorph IV, incorporate the subject matter of claim 3 and to add the unit cell parameters and unit cell volume found at page 6 of the specification. Claim 1 has also been amended to remove the words "stable" and "about".

Claim 2 has been amended to recite that the tiagabine hydrochloride is Polymorph IV and to remove the word "stable".

Claim 3 has been amended to recite that the tiagabine hydrochloride is Polymorph IV, to remove the word "stable".

Claim 4 has been amended to depend from independent claim 1, to recite that the tiagabine hydrochloride is Polymorph IV, and to remove the word "stable".

As a result, claims 1, 2, 3, 4, 9-12 and 16 are now pending in this application; claims 5-8, 13-16, and 17-18 are cancelled; and claims 9-12 and 16 are currently withdrawn from consideration.

Each of the above objections and rejections are dealt with in turn.

Applicants are also enclosing a **Rule 132 Declaration** and **Exhibits I to VI** in response to arguments made in the Office Action of August 29, 2008.

Exhibit I is the XRD of Batch 7022/F/641/12 prepared according to Example 3 of U.S. Patent 5,958,951 (Arndt et al.).

Exhibit II is the XRD of Batch 7022/F/641/13 prepared according to Example 1 of U.S. Patent 5,958,951 (Arndt et al.)

Exhibit III is the XRD of Batch 7022/F/641/06E prepared according to the prior art process described in Point Number 8 of the **Rule 132 Declaration** of Dr. K. Srinivasu.

Exhibit IV is a copy of a letter from Professor T. N. Guru Row describing that sample 7022/F/641/06E is identical to the one reported in the literature and that sample PN 411672 (Applicants' sample) is a new polymorph of tiagabine anhydrous.

Exhibit V contains the experimental details for recrystallizing tiagabine hydrochloride form acetone.

Exhibit VI is XRD pattern of tiagabine hydrochloride acetone solvate.

Objections to the Specification

I. The disclosure was objected to as missing a section entitled "Brief Description of the Drawings".

The specification has been amended by inserting a section entitled "Brief Description of the Drawings" immediately before the section entitled "Detailed Description of the Invention". Support for the brief description of Figure 1 is found at page 3 of the specification and in the caption of Fig. 1. Support for the brief description of Figure 2 is found at page 3 of the specification and in the caption of Fig. 2. Support for the brief description of Figure 3 is found at page 7 of the specification and in the caption of Fig. 3. Support for the brief description of Figure 4 is found at page 8 of the specification and in the caption of Fig. 4. Support for the brief description of Fig. 5 is found at page 8 of the specification and in the caption of Fig. 5.

Applicants believe that these amendments overcome these objections.

Objections to the Claims

II. Claims 1-4 were objected to containing non-elected subject matter. The Office Action asserts that the non-elected subject matter consists of species that are not in the election denoted above.

Claims 1, 2 and 3 have been amended to recite that the new compound is Tiagabine hydrochloride Polymorph IV. Claim 1 has been amended to incorporate the subject matter of claim 3 at page 6 of the Specification. Claim 4 has been amended to depend from claim 1. Applicants believe that these Claims 1-4 now conform to the election of species.

§112 Rejections of the Claims

III. Claims 1 and 4 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action asserts that the "abbreviated pattern" is insufficient to identify the claimed polymorph.

Applicants believe that the amendment to claim 1 inserting the unit cell parameters of anhydrous tiagabine Polymorph IV overcomes this rejection. In addition to the "abbreviated

XRD data", claim 1 now also provides the unit cell parameters of anhydrous tiagabine Polymorph IV. Applicants believe that incorporation of the unit cell data provides any additional written description of Tiagabine hydrochloride Polymorph IV necessary to comply with 35 U.S.C. § 112 first paragraph.

Applicant's would further like to point out that U.S. Patent No. 5,985,951 cited in this rejection discloses "abbreviated XRD data", and recites such data in claims 1 and 2. Applicants believe that if the "abbreviated" XRD data in the '951 patent is good enough for the PTO to cite against Applicants in the Office Action, then "abbreviated" XRD data should be good enough for Applicants to recite in the claims.

Claim 4 has been amended to depend from amended claim 1.

Applicants believe that these amendments overcome the rejection of claims 1 and 4 under 35 U.S.C. § 112 first paragraph. Reconsideration withdrawal of the rejection is earnestly requested.

IV. Claims 1-4 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Office Action asserts that the term "about" is a relative term and renders claim 1 indefinite and is not defined in the specification. The Office Action also asserts that the term "stable" is not defined by the claims or the specification.

Applicants believe that the amendments to claims 1, 2, 3 and 4 overcome this rejection. Claim 1 has been amended to remove the term "about". Claims 2, 3, and 4 have been amended to delete the term "stable".

Applicants believe that these amendments overcome the rejection over 35 U.S.C. § 112 second paragraph. Reconsideration withdrawal of the rejection is earnestly requested.

Rejections of Claims Under 35 U.S.C. §§102(b)/103(a)

V. Claims 1, 3, and 4 were rejected under 35 U.S.C. § 102(b) for anticipation by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Ahrndt et al. (U.S. Patent No. 5,958,951). The Office Action asserts that Figure 8 of the '951 patent has the same XRD pattern

as set forth in Applicants' claim 1. The Office Action admits that the '951 patent does not teach the unit cell parameters or the particle size of the disclosed polymorph, but argues that the polymorph of tiagabine hydrochloride disclosed in the '951 patent and that prepared by Applicants would be the same. The Office Action concludes by requesting that Applicants provide evidence of how their claimed Polymorph IV is different (or unobvious from) the polymorph disclosed in the '951 patent.

Claims 1, 3, and 4 have been amended as described above. However, to the extent that the rejection still applies to these claims, Applicants respectfully traverse this rejection.

Applicants respectfully assert that the specification already provides the evidence of the differences between Applicants' tiagabine Polymorph IV and the polymorph of tiagabine disclosed in the '951 patent. Examiner's attention is directed to page 3, paragraph 1 of the specification where Applicants state that they followed the claimed process of the '951 patent to prepare tiagabine hydrochloride Polymorph II, and report unit cell parameters for this polymorph. The comparison below of the unit cell parameters of tiagabine hydrochloride polymorph II reported on page 3 of the specification with those of tiagabine hydrochloride Polymorph IV reported by Applicants on page 6 of the specification clearly demonstrates that the two polymorphs are different.

Cell Parameters of Tiagabine Hydrochloride Polymorph II Prepared as Claimed in the '951 Patent.		**Cell Parameters of Tiagabine Hydrochloride Polymorph IV Prepared by Applicants.**	
a = 7.775(7)Å	$\alpha = 78.38(9)°$	a = 10.788(3)Å	A = 97.65(2)°
b = 11.10(1)Å	$\beta = 75.88(8)°$	b = 11.492(2)Å	B = 108.92(2)°
c = 14.33(2) Å	$\gamma = 89.21(9)°$	c = 14.799(4)Å	$\gamma = 101.86(2)°$
Vol. 1173.96 $Å^3$		Vol. 1658.63$Å^3$	

Examiner's attention is directed to the enclosed **Declaration under 37 C.F.R. 1.132** paragraphs 6, 7, 8, and 9 and Exhibit IV, where Dr. K. Srinivasu declares that under his direction, his laboratory prepared Tiagabine hydrochloride according to the process claimed in

the '951 patent and found it to be identical to that disclosed in the '951 patent. This material along with a sample of Tiagabine hydrochloride Polymorph IV, prepared as disclosed in U.S. Patent Application Serial No. 10/583,805, was submitted to Professor T. N. Guru Row for XRD analysis. Professor Guru Row found the two powdered samples are different and belong to two different phases. In addition Professor Guru Row found that the unit cell parameters of Applicants' sample of tiagabine hydrochloride Polymorph IV were different from that prepared as disclosed in the '951 patent. (See enclosed Exhibit IV). This further demonstrates that Applicants; tiagabine hydrochloride Polymorph is different from that disclosed in the '951 patent.

In view of the above amendments and remarks, Applicants believe that the rejection of claims 1, 3, and 4 as anticipated/obvious under 35 U.S.C. §§102(b)/103(a) has been fully addressed. Reconsideration withdrawal of the rejection of claims 1, 3, and 4 over Ahrndt et al. is respectfully requested.

VI. Claims 1-4 were rejected under 35 U.S.C. § 102(b) for anticipation by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Andersen et al. (*J. Med. Chem.* **1993,** *36*, 1716-1725, pg. 1717 and 1722, 2nd column). The Office action alleges that Andersen et al. teaches a solid form of tiagabine hydrochloride obtained by recrystallization from acetone. The Office Action admits that Andersen et al. does not teach the specific polymorph because the X-ray diffraction data is not disclosed. The Office action concludes that in the absence of further evidence, the tiagabine hydrochloride produced by Andersen et al. by recrystallization from acetone would be expected to have the same crystal polymorph as Applicants' tiagabine hydrochloride. The Office Action concludes by requesting Applicants to provide a showing of how their claimed Polymorph IV is different (or unobvious from) the polymorph disclosed in the Andersen et al. reference.

Claims 1-4 have been amended as described above. However, to the extent that the rejection still applies to these claims, Applicants respectfully traverse this rejection.

Applicants direct the Examiner's attention to the analytical data for tiagabine hydrochloride prepared by Andersen et al. by recrystallization by recrystallization from acetone

as reported at page 1722, column 2, 2nd line from the bottom. It shows that Andersen discloses that tiagabine hydrochloride prepared from acetone is a solvate having the formula $C_{20}H_{25}NO_2S_2{\cdot}0.75C_3H_6O$.

Applicants further direct the Examiner's attention to U.S. Patent 5,354,760 (Petersen et al.) cited on page 1 of the present Application and submitted in the IDS filed August 25, 2006. At column 1, lines 49-52, the '760 patent reads: "Use of alternative organic solvents such as acetonitrile, butyl acetate, toluene, acetone, dichloromethane etc. also gives products containing various amounts of the used crystallizing solvent." The patent further discloses at column 1, line 67 to column 2, line 1, "It has now been found that water can be used as a crystallizing solvent for this compound giving very reproducible results of a monohydrate crystal form." Applicants believe that these disclosures in U.S. 5,354,760 provide the showing requested in the Office Action that Applicants' tiagabine hydrochloride Polymorph IV cannot be the same polymorph obtained by Andersen et al. by recrystallization from acetone.

Examiner's attention is directed to the enclosed **Declaration under 37 C.F.R. 1.132** paragraphs 10 and 11, where Dr. K. Srinivasu declares that under his direction, his laboratory prepared Tiagabine hydrochloride according to the process disclosed in Exhibit V and found it to be a Tiagabine hydrochloride acetone solvate. This material along with a sample of Tiagabine hydrochloride Polymorph IV, prepared as disclosed in U.S. Patent Application Serial No. 10/583,805, was analyzed by XRD. The two compounds were found to have different XRD pattern (See enclosed Exhibit V). This further demonstrates that Applicants; tiagabine hydrochloride Polymorph is different from that disclosed in the Andersen et al paper.

In view of the above amendments and remarks, Applicants believe that the rejection of claims 1-4 as anticipated/obvious under 35 U.S.C. §§102(b)/103(a) has been fully addressed. Reconsideration withdrawal of the rejection of claims 1-4 over Andersen et al. is respectfully requested.

VII. Claims 1-4 were rejected under 35 U.S.C. § 102(b) for anticipation by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Gronvald et al. (U.S. Patent No. 5,010,090). The Office Action asserts that the '090 patent teaches a solid form of tiagabine hydrochloride

obtained by recrystallization from ethyl acetate. The Office Action admits that the '090 patent does not teach the specific polymorph because the X-ray diffraction data is not disclosed. The Office action concludes that in the absence of further evidence, the tiagabine hydrochloride produced as disclosed in the '090 patent by recrystallization from ethyl acetate would be expected to have the same crystal polymorph as Applicants' tiagabine hydrochloride. The Office Action concludes by requesting Applicants to provide a showing of how their claimed Polymorph IV is different (or unobvious from) the polymorph disclosed in the '090 patent.

Claims 1-4 have been amended as described above. However, to the extent that the rejection still applies to these claims, Applicants respectfully traverse this rejection.

Applicants direct the Examiner's attention to U.S. Patent 5,958,951 (Arndt et al.) cited above and on page 1 of the present Application. At column 1, line 39-49, the '951 patent states "The alternative product, which is disclosed in the U.S. Pat. No. 5,010,090 (column 8, line 62) can only be prepared through a labour intensive process as described, using ethyl acetate. Furthermore analysis has shown that products manufactured by this process contain unwanted amounts of the crystallizing solvent. Other organic solvents may be used in the isolation of the product, but organic solvents will often form chlathrates, i.e. solvates of tiagabine hydrochloride and the resp. organic solvent". Applicants believe that this disclosure in U.S. 5,958,951 provides the showing requested in the Office Action that Applicants' tiagabine hydrochloride Polymorph IV cannot be the same polymorph obtained by Gronvald et al. by recrystallization from ethyl acetate.

Applicants further direct the Examiner's attention to U.S. Patent 5,354,760 (Petersen et al.) cited on page 1 of the present Application and submitted in the IDS filed August 25, 2006. At column 1, lines 33-51 the '760 patent discloses that tiagabine hydrochloride can be recrystallized from ethyl acetate. At column 1, lines 46-48, the '760 patent states "Furthermore analysis has shown that products manufactured by this process contain unwanted amounts of the crystallizing solvent ethyl acetate." Additionally, at column 1, lines 49-52, the '760 patent continues, "Use of alternative organic solvents such as acetonitrile, butyl acetate, toluene, acetone, dichloromethane etc. also gives products containing various amounts of the used crystallizing solvent." The patent further discloses at column 1, line 67 to column 2, line 1, "It

has now been found that water can be used as a crystallizing solvent for this compound giving very reproducible results of a monohydrate crystal form." Applicants believe that these disclosures in U.S. 5,354,760 provide additional showing as requested in the Office Action that Applicants' tiagabine hydrochloride Polymorph IV cannot be the same polymorph obtained by Gronvald et al. by recrystallization from ethyl acetate.

Examiner's attention is directed to the enclosed **Declaration under 37 C.F.R. 1.132** paragraphs 12 and 13, where Dr. K. Srinivasu declares that under his direction, his laboratory attempted to prepared Tiagabine hydrochloride and found that it required an inordinately large amount of solvent and gave an impure product, brown in color and having a blue tinge.

In view of the above amendments and remarks, Applicants believe that the rejection of claims 1-4, as anticipated/obvious under 35 U.S.C. §§102(b)/103(a) has been fully addressed. Reconsideration withdrawal of the rejection of claims 1, 3, and 4 over Gronvald et al. is respectfully requested.

Additional Remarks Regarding the Rejections of Claims Under 35 U.S.C. §§102(b)/103(a)

Applicants have discovered that their preparation of tiagabine hydrochloride unexpectedly results in the new Polymorph IV of tiagabine hydrochloride. This process, disclosed on page 5 of Applicants' Specification, "comprises dissolving tiagabine hydrochloride in an organic solvent or a mixture of organic solvent and an organic non-solvent and adding a sufficient amount of organic anti-solvent to the solution to cause crystallization at a selected temperature wherein the selected temperature is such that form IV of tiagabine hydrochloride is crystallized preferably the selected temperature may be +35°C or -10°C. The solution may be optionally cooled at 0°C to 10°C for further crystallization. The novel Polymorphic IV of tiagabine hydrochloride may also be prepared by crystallizing tiagabine hydrochloride from a solution of tiagabine hydrochloride in an organic solvent or a mixture of organic solvent and organic anti-solvent wherein the solution is seeded with tiagabine hydrochloride Polymorph IV seed crystals." The material is then dried.

None of the three cited references describes Applicants' process of preparing Polymorph IV of tiagabine hydrochloride. Given the disclosures of the three cited references,

one skilled in the art of preparing tiagabine hydrochloride by recrystallization from solvents would not have expected to obtain tiagabine hydrochloride Polymorph IV. Thus, the three cited references also teach away from Applicants' unexpected and non-obvious discovery of tiagabine hydrochloride Polymorph IV.

CONCLUSION

Applicants respectfully submit that all pending claims are now in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's representative at (612) 373-6961 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on February 25, 2009.

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